REMARKS

Upon entry of this amendment, claims 1, 3-4, 7-8, 10-23, 32-33, and 50-52 will be pending in this application and presented for examination. Claims 1, 3, 7, 10, 14, 15, 17, 18 , 19, and 32 have been amended. Claims 2, 5-6, 9, 24-31 and 34-49 have been canceled without prejudice or disclaimer. Claims 50-52 are newly added. No new matter has been entered with the foregoing amendments and new claims. Reconsideration in view of the remarks and amendments is respectfully requested.

I. FORMALITIES

Claim 1 has been amended by incorporating the features of claim 2. Accordingly, claim 2 has been cancelled without prejudice. Claims 3, 7, 10, 14-15, 17, and 32 have been amended to reduce their multiple dependencies. Claim 18 has been amended to more particularly point out and distinctly claim the subject matter therein.

Claims 50-52 are newly added. Support is found, for example, in Figure 3. In view of the foregoing support and remarks, Applicants respectfully request that the Examiner enter the amendments and new claims.

II. THE INVENTION

The present invention provides *inter alia*, conformationally constrained, monomeric cyclic peptide analogues of a B-chain of a relaxin superfamily member protein which binds to a biological target of the relaxin superfamily protein, the protein being selected from insulin, IGF-I, IGF-II, relaxin 1, relaxin 2, relaxin 3, INSL3, INSL4, INSL5 or INSL6.

III. RESTRICTION REQUIREMENT

Applicants elected Group 1 drawn to claims 1-23, and 32-33 with traverse. Applicants elected the monomeric cyclic peptide INSL3 (SEQ ID NO: 7) of claim 3. Claim 3 is clearly drawn to a monomeric cyclic peptide B-chain analogue made from the sequence of SEQ ID NO: 7 (a dependent claim incorporates all the limitations of an independent claim 35 U.S.C. §

112, fourth paragraph). Contrary to the Examiner's statements, the cyclic peptide of claim 3 is not linear. The further species election of claims 17 and 19 were included in the species election as required by the Examiner.

As will be clear from the discussion below, the cyclic peptide of claim 3 is not anticipated by Schwabe *et al.* The Examiner has therefore improperly withdrawn claims drawn to the elected invention, including 2, 4-33 as these claims are drawn to cyclic peptides of a B-chain and are not linear peptides. Applicants assert that the claims were improperly withdrawn as the elected species of claim 3 is novel over the prior art. As such, the withdrawn claims readable on the elected invention must be rejoined and examined on their merits.

IV. OBJECTION TO CLAIMS 32-33

Claims 32-33 were objected to as being multiple dependent claims dependent on another multiple dependent claim. Applicants have amended claim 32 to remove the multiple dependency. Therefore, Applicants respectfully request that the Examiner withdraw the objection.

V. REJECTION UNDER 35 U.S.C. § 112, SECOND PARAGRAPH

The Examiner rejected claims 1 and 3 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite. To the extent the rejection is applicable to the amended set of claims, Applicants respectfully traverse the rejection.

The Examiner states that claim 1 and dependent claim 3 are drawn to monomeric cyclic peptide analogues. According to the Examiner, claim 3 states that the analogues are modified from a sequence set forth in SEQ ID NO:7. The Examiner alleges that the metes and bounds of the claims are unclear, however, as there is no accepted nor specific definition to identify analogues and their degree or type of modification.

In order to expedite prosecution in the present case, claim 1 has been amended to incorporate the features of claim 2. Claim 1 (and claim 3 by its dependency) now recites the following feature:

> and wherein the analogue is produced by modification of a turn or loop moiety of the B-chain of the relaxin superfamily protein, the modification involving selection of at least a first and a second amino acid residue with an alpha-helix or beta-strand carbon separation distance of less than six angstroms and cross-linking the first and second amino acids, wherein the cross-link conformationally constrains the analogue.

The specification clearly teaches how cyclic peptide analogues in accordance with claim 1 are produced (for example at page 13, line 12, bridging to page 14, line 5). Further, Examples 1 and 2 (pages 23 to 26) demonstrate the production of cyclic peptide analogues of the B-chain of two members of the relaxin superfamily, relaxin 1 and INSL3 in which, in accordance with claim 1 as amended, the analogue is produced by modification of a turn or loop moiety wherein the modification involves selection of at least a first and a second amino acid residue with an alpha-helix or beta-strand carbon separation distance of less than six angstroms and wherein the first and second amino acid residues are cross-linked, the cross-link conformationally constraining the analogue. The sequences of these analogues are shown in Figure 3 of the present specification. Specific binding of the analogues is demonstrated in Figures 1 (receptor LGR8) and 2 (receptor LGR7), while antagonistic activity of the cINSL3a analogue against INSL3 at LGR8 is shown in Figure 4.

In view of the claim amendments and remarks, Applicants assert that the claims are clear and definite. Accordingly, Applicants request that the Examiner withdraw this rejection.

VI. REJECTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH

Claims 1 and 3 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. In brief, the Examiner argues that that the claims are broadly described without the requisite number of species. To the extent the rejection is applicable to the amended set of claims, Applicants respectfully traverse the rejection.

Applicants are claiming the modification of 10 discrete starting molecules to make monomeric, cyclic peptide analogues, which starting molecules are the very well defined B-chains of insulin, IGF-I, IGF-II, relaxin 1, relaxin 2, relaxin 3, INSL3, INSL4, INSL5 and INSL6 (SEQ ID NO: 1-10). Further, these monomeric, cyclic peptide analogues are functionally defined as being able to bind to a biological target of the relaxin superfamily protein, wherein the biological target is selected from specific insulin receptors, *i.e.*, IGFR-I, IGFR-II, LGR7 and LGR8. Further, the method of modification is well defined as being a turn or loop moiety of the B-chain of the relaxin superfamily protein, involving selection of at least a first and a second amino acid residue with an alpha-helix or beta-strand carbon separation distance of less than six angstroms and cross-linking the first and second amino acids, wherein the cross-link conformationally constrains the analogue.

Further, the specification clearly teaches how cyclic peptide analogues in accordance with claim 1 are produced (for example at page 13, line 12, bridging to page 14, line 5). Further, Examples 1 and 2 (pages 23 to 26) demonstrate the production of cyclic peptide analogues of the B-chain of two members of the relaxin superfamily, relaxin 1 and INSL3 in which, the analogue is produced by modification of a turn or loop moiety wherein the modification involves selection of at least a first and a second amino acid residue with an alpha-helix or beta-strand carbon separation distance of less than six angstroms and wherein the first and second amino acid residues are cross-linked, the cross-link conformationally constraining the analogue.

Examples 1 and 2 (pages 23 to 26) demonstrate the production of cyclic peptide analogues of the B-chain of two members of the relaxin superfamily, relaxin 1 and INSL3 in which the analogue is produced by modification. The sequences of these analogues are shown in Figure 3 of the present specification, along with an additional member. Specific binding of the analogues is demonstrated in Figures 1 (receptor LGR8) and 2 (receptor LGR7), while antagonistic activity of the cINSL3a analogue against INSL3 at LGR8 is shown in Figure 4.

Regardless of the modification and/or substitutions, the analogue must still be linked to conformationally constrain the molecule and the molecule must bind to a biological

target of a relaxin superfamily protein selected from insulin receptors, IGFR-I, IGFR-II, LGR7 and LGR8.

> Under MPEP § 2163:
>
> The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. See *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406.

In the present case, the written description requirement is clearly satisfied as the claimed genus has a representative number of species by actual reduction to practice, the drawings of the molecular structure are clearly set forth in Figure 3 and the specific physical binding of the analogues is demonstrated in Examples 1 and 2. In Figures 1 and 2, the binding to receptors LGR8 and LGR7 is illustrated, while antagonistic activity of the cINSL3a analogue against INSL3 at LGR8 is shown in Figure 4. Clearly, Applicants have satisfied the requirements of 35 U.S.C. § 112, first paragraph. Accordingly, Applicants respectfully request that the Examiner withdraw the rejection.

VII. REJECTION UNDER 35 U.S.C. § 101

Claims 1 and 3 were rejected under 35 U.S.C. § 101 as allegedly being directed to non-statutory subject matter. According to the Examiner, the claimed subject matter reads on a product of nature. To the extent the rejection is applicable to the amended set of claims, Applicants respectfully traverse the rejection.

Claim 1 has been amended to recite that the monomeric, cyclic peptide analogue of a B-chain of a relaxin superfamily member protein which binds to a biological target of the relaxin superfamily protein, and modulates an activity of the biological target, wherein the relaxin superfamily protein is selected from insulin, IGF-I, IGF-II, relaxin 1, relaxin 2, relaxin 3,

INSL3, INSL4, INSL5 and INSL6, the biological target being selected from insulin receptors, IGFR-I, IGFR-II, LGR7 and LGR8:

> is produced by modification of a turn or loop moiety of the B-chain of the relaxin superfamily protein, the modification involving selection of at least a first and a second amino acid residue with an alpha-helix or beta-strand carbon separation distance of less than six angstroms and cross-linking the first and second amino acids, wherein the cross-link conformationally constrains the analogue.

Applicants assert that the claimed subject matter of a monomeric, cyclic peptide analogue of a B-chain of a relaxin superfamily protein with the claimed modification precludes that the subject matter from being found in nature. As is explained more fully below, Schwabe *et al* teach proteins having both an A and B chain and not a cyclic peptide of the B-chain. Accordingly, Applicants respectfully request that the rejection be withdrawn.

VIII. REJECTION UNDER 35 U.S.C. § 102(b)

The Examiner rejected claims 1 and 3 under 35 U.S.C. § 102(b) as allegedly being anticipated by U.S. Patent No. 5,911,997 (Schwabe *et al.*). The Examiner states that Figure 1 teaches a peptide identified as the relaxin-like factor. Accordingly to the Examiner, the peptide includes the B-chain portion identified as SEQ ID NO:4 which includes the primary sequence (without the disulfide bonds) identified as SEQ ID NO:7 of the instant invention. According to the Examiner, the peptide of Schwabe *et al.* is an analog of SEQ ID NO:7 (a linear peptide) of the instant invention since the peptide of Schwabe *et al.* includes disulfide bonds and cyclization thus meeting the limitations of claims 1, and 3 of the instant invention. To the extent the rejection is applicable to the amended set of claims, Applicants respectfully traverse the rejection.

Under MPEP § 2131:

> [a] claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987).

The Examiner has apparently misunderstood the claimed invention. The Examiner's attention is respectfully directed to page 1, lines 19-20 of the Background of the Invention:

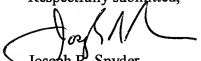
> Relaxin is an insulin-like peptide having two separate chains (A and B) joined by two interchain and one intrachain disulfide bond.

The foregoing is what is taught by Schwabe *et al.* as RLF. Schwabe neither discloses nor contemplates a monomeric cyclic peptide analogue of a relaxin superfamily member B-chain. Schwabe *et al.* describe the sequence for RLF (relaxin-like-factor; Ley I-L protein). Figure 1 of Schwabe *et al.*, as referred to by the Examiner, does not teach a cyclic B-chain peptide analogue, but rather simply shows the joining of the A and B-chain of RLF via two interchain and one intrachain disulfide bonds, which is characteristic of all members of the relaxin superfamily. This is simply the well known means by which the A and B-chains naturally associate *in vivo*.

As Schwabe *et al.* do not teach a monomeric, cyclic peptide analogue of a B-chain of a relaxin superfamily member protein which is produced by modification of a turn or loop moiety of the *B-chain* of the relaxin superfamily protein, the claims are not anticipated. Accordingly, Applicants request that the Examiner withdraw the rejection.

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested. If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 925-472-5000.

Respectfully submitted,



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